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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/074,247	02/14/2002	Lawrence M. Nogee	001107.00229	5075

22907 7590 09/30/2003

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SWITZER, JULIET CAROLINE

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 09/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/074,247	NOGEE ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-58* is/are pending in the application.

4a) Of the above claim(s) *1-8,11-13,18 and 21-58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9,10,14-17,19 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group II, and further election of nucleotide 243 as the SNP in the paper filed 7/15/03 is acknowledged. Applicant is correct in noting that claim 20 should also have been included in group II. Claims 9-10, 14-17, and 19-20 are examined herein. Claims 11-13 and 21-23, which were originally included in group II, are withdrawn from prosecution as they specifically recite only a non-elected SNP.

2. It is noted that claims 9, 14-17, and 19 are drawn to polynucleotides and reagents that are generic to any SNP in the human surfactant protein C gene that is associated with interstitial lung disease. These claims have been examined as they are written (full breadth), while claims 10 and 20 which recite particular SNPs have been examined only with regard to the elected SNP, at position 243 of SEQ ID NO: 1.

3. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 9, 10, 14 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Halverson *et al.* (US 5874217).

Halverson *et al.* teach a single-stranded polynucleotide comprising 12 contiguous nucleotides of a mutant allele of a human surfactant protein C gene, wherein the 12 contiguous nucleotides comprise a SNP associated with an intersitital lung disease.

Specifically, Halverson *et al.* teach a primer that they identify as SEQ ID NO: 22, and nucleotides 1-12 of this sequence are identical to nucleotides 236-247 of instant SEQ ID NO: 1 (Col. 7 and sequence listing). A primer is a single stranded polynucleotide, and this primer taught by Halverson *et al.* comprises 12 contiguous nucleotides of a mutant allele of a human surfactant protein C gene. The open claim language "comprising" means that the claimed polynucleotide has 12 nucleotides from a contiguous nucleotides of a mutant allele of a human surfactant protein C gene, but may also have any additional flanking sequence. The 12 contiguous nucleotide are considered to "comprise a SNP associated with an interstitial lung disease" insofar as to "comprise a SNP" means to overlap with a nucleotide of SEQ ID NO: 1 that has been identified as being a polymorphic position. In the instant case, the polynucleotide taught by Halverson *et al.* "comprises" the SNP located at position 243 of instant SEQ ID NO: 1 (limitation of claim 10).

With respect to claim 14, Halverson *et al.* teach a single-stranded polynucleotide which further comprises a detectable label, teaching that for any of the given primer pairs a label may be conjugated to one or both of the primers (Col. 5, lines 23-24).

With respect to claim 15, the SNP is considered to be at the "5' end" of the polynucleotide because it is in the eighth position of the polynucleotide taught by Halverson *et al.* and this is at the 5' end relative to the center of the polynucleotide.

6. Claim 17 is rejected under 35 U.S.C. 102(b) as being anticipated by the New England Biolabs Catalog, 1996/1997, pages 12 and 28.

New England Biolabs (NEB) teach a kit comprising a reagent for detecting a SNP in a mutant allele of a human surfactant protein C gene, wherein the SNP is associated with interstitial lung disease; and instructions for a method of detecting the SNP.

Specifically, NEB teaches a kit comprising the restriction endonuclease BstN I (see p. 28, which discloses the kit) and directions for using BstN I (see p. 12 which teaches that the Technical Data Card included with the kit discusses at least appropriate incubation temperature for using the enzymes, i.e. directions for using the kit to detect restriction sites). This reagent is inherently considered a reagent that for detecting a SNP in a mutant allele of a human surfactant protein C gene, since the specification teaches that the mutation at the intronic nucleotide immediately 3' of nucleotide 460 of SEQ ID NO: 1 (460+1) is detectable by BstN I.

Furthermore, it is noted that the actual content of the instructions "i.e. for a method of detecting the SNP" is considered to be a statement of intended use for the claimed kits. In the Opinion Text of *In re Haller*, 73 USPQ 403 (CCPA 1947), the court stated "Whether the statement of intended use appears merely in the claim or in a label on the product is immaterial so far as the question of patentability is concerned." The instructions of the instant kit are not considered to distinguish the claimed kits over the prior art as they are merely a statement of intended use included with the claimed product.

Thus, the kit taught by the New England Biolabs is considered to meet all of the structural limitations of the instantly rejected claim.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Halverson *et al.* in view of Adams *et al.* (US 5641658).

Halverson *et al.* teach a single-stranded polynucleotide comprising 12 contiguous nucleotides of a mutant allele of a human surfactant protein C gene, wherein the 12 contiguous nucleotides comprise a SNP associated with an interstitial lung disease.

Specifically, Halverson *et al.* teach a primer that they identify as SEQ ID NO: 22, and nucleotides 1-12 of this sequence are identical to nucleotides 236-247 of instant SEQ ID NO: 1

(Col. 7 and sequence listing). A primer is a single stranded polynucleotide, and this primer taught by Halverson *et al.* comprises 12 contiguous nucleotides of a mutant allele of a human surfactant protein C gene. The open claim language "comprising" means that the claimed polynucleotide has 12 nucleotides from a contiguous nucleotides of a mutant allele of a human surfactant protein C gene, but may also have any additional flanking sequence. The 12 contiguous nucleotide are considered to "comprise a SNP associated with an interstitial lung disease" insofar as to "comprise a SNP" means to overlap with a nucleotide of SEQ ID NO: 1 that has been identified as being a polymorphic position. In the instant case, the polynucleotide taught by Halverson *et al.* "comprises" the SNP located at position 243 of instant SEQ ID NO: 1.

Halverson *et al.* do not teach the single stranded polynucleotide which is bound to a solid support, as recited in instant claim 16.

Adams *et al.* teach methods of amplification using primers bound to solid supports for use in PCR amplification processes (Cols. 3-4). It would have been prima facie obvious at the time the invention was made to have included the single-stranded polynucleotide taught by Halverson *et al.* on a solid support such as is taught by Adams *et al.* One would have been motivated to have included the primer taught by Halverson *et al.* on a solid support as taught by Adams *et al.* in order to take advantage of the solid phase amplification assays taught by Adams *et al.*, especially since Adams *et al.* teach that the use of their methods and products "allow the performance of multiple simultaneous amplification reactions for rapid analysis of nucleic acids..." and that such reactions "do not require the presence of an external reaction chamber, or the presence of use of gels for the analysis of the amplification product (Col. 3, lines 25-30)."

Thus, in light of the teachings of Halverson *et al.* in view of Adams *et al.*, the instant invention is *prima facie* obvious.

10. Claims 17, 19 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Halverson *et al.* in view of Ahern (The Scientist, Vol. 9, #15, p. 20, July 1995, provided as HTML print out pages 1-5).

Halverson *et al.* teach a kit comprising a reagent for detecting a SNP in a mutant allele of a human surfactant protein C gene, wherein the reagent is a single-stranded polynucleotide comprising 12 contiguous nucleotides of the mutant allele, wherein the 12 contiguous nucleotides comprise the SNP.

Specifically, Halverson *et al.* teach a primer that they identify as SEQ ID NO: 22, and nucleotides 1-12 of this sequence are identical to nucleotides 236-247 of instant SEQ ID NO: 1 (Col. 7 and sequence listing). A primer is a single stranded polynucleotide, and this primer taught by Halverson *et al.* comprises 12 contiguous nucleotides of a mutant allele of a human surfactant protein C gene. The open claim language "comprising" means that the claimed polynucleotide has 12 nucleotides from a contiguous nucleotides of a mutant allele of a human surfactant protein C gene, but may also have any additional flanking sequence. The 12 contiguous nucleotide are considered to "comprise a SNP associated with an interstitial lung disease" insofar as to "comprise a SNP" means to overlap with a nucleotide of SEQ ID NO: 1 that has been identified as being a polymorphic position in the claims. In the instant case, the polynucleotide taught by Halverson *et al.* "comprises" the SNP located at position 243 of instant SEQ ID NO: 1 (limitation of claim 19). Further, Halverson *et al.* teach that this primer may be provided in a kit (Col. 6, lines 22-30).

Halverson *et al.* do not teach a kit which includes instructions.

Ahern teaches biochemical reagent kits, and teaches that such kits are convenient for scientists because they put the reagents needed for a particular assay all together for a scientist to use (p. 4). Ahern further teaches that biochemical kits provide a further advantage to customers because they provide detailed instructions to follow (p. 4).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to have modified the kit taught by Halverson *et al.* so as to have included instructions, as taught by Ahern. One would have been motivated to make such an inclusion in order to have provided an additional advantage to users of the kit, that is to direct them as to how to use the reagents contained in the kit. Furthermore, it is noted that the actual content of the instructions "i.e. for a method of detecting the SNP" is considered to be a statement of intended use for the claimed kits. In the Opinion Text of *In re Haller*, 73 USPQ 403 (CCPA 1947), the court stated "Whether the statement of intended use appears merely in the claim or in a label on the product is immaterial so far as the question of patentability is concerned." The content of the instructions of the instant kit are not considered to distinguish the claimed kits over the prior art.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 9, 10, 14, 15, 16, 17, 19, and 20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter

which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the Invention

The invention concerns single stranded polynucleotides comprising portions of a mutant allele of a human surfactant protein C gene, wherein the polynucleotides "comprise a SNP associated with interstitial lung disease." Additional claims are directed at reagents for detecting such SNPs. The invention, as claimed, is directed towards products which, as recited in the claims encompass portions of nucleic acids associated with interstitial lung disease or detect such portions of nucleic acids. Critical to using the claimed products is the establishment of an association between particular single nucleotide polymorphisms and "interstitial lung disease."

Breadth of the Claims

With regard to the physical structure of the products themselves, claim 9 encompasses a single-stranded polynucleotide comprising 12 contiguous nucleotides of a "mutant allele" of a human surfactant protein C gene, wherein the 12 contiguous nucleotides comprise a SNP associated with interstitial lung disease. While the claim recites that the 12 contiguous nucleotides must be from a "mutant allele" of a human surfactant protein C gene, the claim does not require that the 12 contiguous nucleotides overlap with the mutant SNP, only that the 12 contiguous nucleotide overlap with a SNP associated with interstitial lung disease (as disclosed in the specification there are many putative associated polymorphisms within the gene). For example, a human surfactant protein C gene may be mutated at position 5, but the 12 contiguous nucleotides that are comprised within the claimed invention could be positions 15-26 of the gene which overlap with hypothetical polymorphic position 25, which, hypothetically is disclosed as

being associated with interstitial lung disease, even if the particular human surfactant protein C gene is not mutated at position 25. The claim does not recite any polymorphisms in particular, and thus encompasses polynucleotides that overlap with any polymorphic position in the human surfactant C protein gene, provided the polymorphism is "associated with interstitial lung disease." In addition, the breadth of the claim encompasses SNPs within the human surfactant protein C gene that are associated with any "interstitial lung diseases" which include chronic pneumonitis of infancy, a variety of disorders associated with lung inflammation, pulmonary sarcoidosis, or lymphangitic carcinomatosis (infiltration and obstruction of pulmonary parenchymal lymphatic channels by tumor) (p. 6). These diseases all share in common that they are diseases of the lung interstita, but beyond that they represent a diverse group of diseases which have different causes and etiologies.

Claim 10, recites that the SNP is located at particular positions of SEQ ID NO: 1, with position 243 being elected for prosecution.

Claims 14-16 further define the claimed polynucleotide as comprising a label, having the SNP at the 3' or 5' end, and being on a solid support.

Claim 17 is drawn to a kit comprising a reagent for detecting a SNP in a mutant allele or a human surfactant protein C gene, wherein the SNP is associated with interstitial lung disease, and instruction for a method of detecting the SNP. The reagent of claim 17 encompasses a wide variety of reagents, for example, polynucleotide probes that overlap with the SNP, restriction enzymes, sequencing reagents, labels, etc. The claim does not recite any polymorphisms in particular, and thus encompasses polynucleotides that overlap with any polymorphic position in the human surfactant C protein gene, provided the polymorphism is "associated with interstitial

lung disease." In addition, the breadth of the claim encompasses SNPs within the human surfactant protein C gene that are associated with any "interstitial lung diseases" which include chronic pneumonitis of infancy, a variety of disorders associated with lung inflammation, pulmonary sarcoidosis, or lymphangitic carcinomatosis (infiltration and obstruction of pulmonary parenchymal lymphatic channels by tumor) (p. 6).

Claim 19 depends from claim 17 and recites that the reagent is a single-stranded polynucleotide comprising 12 contiguous nucleotides of a "mutant allele" of a human surfactant protein C gene, wherein the 12 contiguous nucleotides comprise the SNP or the complement of the SNP, and claim 20 recites that the SNP is located at particular positions of SEQ ID NO: 1, with position 243 being elected for prosecution.

Direction in the Specification and Working Examples

The specification teaches thirty two single nucleotide polymorphisms within the human surfactant protein C gene (referred to as the SP-C gene) (Table 1, pages 8-9) and indicates that seventeen of these were found only in patients with "lung disease." The specification does not specify how many patients were screened to obtain this set of polymorphisms, nor does the specification indicate what types of lung diseases were included in the patient sample, which lung diseases the individual SNPS were found in, or in how many patients. For those polymorphisms that were not indicated as being found only in lung diseased patients, the specification does not set forth where they were found (i.e. in what ratio in which types of patients).

The specification asserts that the disclosed SNPS can be used to identify individuals who have a predisposition for developing one of a wide variety of "interstitial lung diseases" which

include chronic pneumonitis of infancy, a variety of disorders associated with lung inflammation, pulmonary sarcoidosis, or lymphangitic carcinomatosis (infiltration and obstruction of pulmonary parenchymal lymphatic channels by tumor) (p. 6). These diseases all share in common that they are diseases of the lung interstita, but beyond that they represent a diverse group of diseases which have different causes and etiologies.

The specification further suggests that "Association of a SNP with interstitial lung disease can be determined, for example, by statistical correlation of a disease phenotype with a particular SNP (p. 9-10)," and suggests some "well known" art methods for making such a determination.

The specification at pages 11-17 provide generic guidance as to obtaining nucleic acid samples and testing for the presence or absence of polymorphisms in nucleic acids.

Example 1 of the specification (p. 18-19) teaches a case patient full-term Caucasian female whose mother was diagnosed as having desquamative interstitial pneumonitis (DIP). The case patient developed respiratory symptoms in room air at 6 weeks of age, and an open lung biopsy showed histological features that most closely resembled cellular or non-specific interstitial pneumonitis. Control lung tissues included donor lung tissue as well as tissue from patients having end-stage pulmonary disease, including bronchopulmonary dysplasia and primary pulmonary hypertension 12

Example 2 of the specification (p. 19-20) teaches the analysis of genomic DNA by direct sequencing of PCR products and restriction analysis. The example teaches that a G to A transition was identified at the first base of intron 4 of the case patient's SP-C gene, and that no other deviations were observed in the case patient's SP-C coding sequences or intron-exon

boundaries. The presence of the mutation was confirmed in the case patient's mother, but was not found in 100 chromosomes from control subjects (p. 20).

Example 3 of the specification teaches that mature SP-C was undetectable in the lung tissue and bronchoalveolare lavage fluid of a case patient but was detected from age matched control patients (p. 21).

The specification does not provide any guidance as to which particular interstitial lung diseases (of the many various possibilities) might be associated with any of the many polymorphisms disclosed herein. The single polymorphism for which the specification provides any particular guidance, it is unclear from the teachings of the specification if the presence of the mutation is in fact indicative of any particular disease, since it was only identified in two related patients, albeit diseased patients. The specification lacks specific guidance that would enable one to conclude that in fact any of the disclosed polymorphisms are "associated with intersitital lung disease" in general (as recited in the claims) or even to conclude that any particular polymorphism disclosed herein is associated with any particular lung disease in general.

State of the Art and Level of Unpredictability

The prior art does not provide any polymorphisms in the human SP-C gene that are associated with interstitial lung disease. However, there is a large body of knowledge in the prior art related to polymorphisms in general, and their association with diseases or disease states. The art is highly unpredictable with regard to the functionality of polymorphic sites in genomic DNA. After a screening assay identifies polymorphisms, it is unpredictable whether any such polymorphisms would be associated with any phenotypic trait, such as a disease state or a physiological state. For example, Hacker et al. were unable to confirm an association between

a gene polymorphism and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (Gut, 1997, Vol. 40, pages 623-627). Even in cases where an association between a particular gene and a disease state is known to exist, such as with the LPL gene and heart disease risk or the β-globin gene and sickle cell anemia, researchers have found that when using SNP (single nucleotide polymorphism analysis) it was difficult to associate SNPs with disease states or to even identify key genes as being associated with disease (Pennisi, Science, 281 (5384):1787-1789). Finally, in some cases where multiple polymorphisms are identified in a gene, some of these are demonstrated to be disease associated and some are not. Blumenfeld et al. (WO 99/52942) disclose a number of polymorphisms in the FLAP gene. While Blumenfeld et al. were able to demonstrate that some of these polymorphisms are associated with patients having asthma but some of these are not (see Figure 3). For example, the marker 10-35/390 was demonstrated to be associated with asthma, with a p value of 0.00229, while the marker 10-33/327 was determined to not have a statistical association with asthma (p=0.294). Thus, even for SNPs within the same gene, it is highly unpredictable as to whether a particular marker will be disease associated.

Indeed, even the post-filing date art reiterates the unpredictability of determining an association between a SNP and a disease state. Hirschhorn *et al.* (Genetics In Medicine, 2002, Vol. 4, No. 2, p. 45-61) performed a review of association studies between single nucleotide polymorphisms and diseases, an found that most reported associations s are not robust, of 166 putative associations which have been studied three or more times only 6 have been consistently replicated, noting that these six are probably the upper limit for the number of consistently

reproducible studies due to publication bias (p. 51, Col. 1). Hirschhorn *et al.* suggest a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn *et al.* caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering their use as diagnostics and prognostics (p. 60, Col. 2).

In the instant case, the low level of reproducibility of association studies and the unpredictability with regard to determining the relationship between SNPs is especially significant as without such a demonstrated association association, one cannot determine that a particular probe or reagent would detect a SNP that is "associated with interstitial lung disease" in general or any interstitial lung disease in particular. The instant specification does not provide a robust association study for the elected SNP (claims 10 and 20), in particular, or for any of the other thirty two SNPs recited in Table 1. Even the study completed with the G to A transition was identified at the first base of intron 4 of the case patient's SP-C gene fails to establish a predictive or associative relationship between the SNP and any particular interstitial lung disease because the SNP was identified in only a single family, and therefore, it cannot be determined from the specification the robustness of the putative association, in light of the high degree of unpredictability in this art.

Furthermore, beyond the high degree of unpredictability of the association of any of the 32 specifically disclosed SNPs and any particular interstitial lung disease or interstitial lung disease in general, it is also noted that most of the elected claims encompass reagents for the detection of any mutant allele of a human surfactant protein C gene that may be associated with

interstitial lung disease, encompassing polynucleotides that comprise portions of the human surfactant protein C gene or reagents for detection of SNPS that are unknown from the specification. The structure and location of these SNPs, as well as their functionality (what disease they are associated with, for example) are not unpredictable, even given that the sequence of the genomic and coding portions of the gene were known. It is not possible to predict where a particular polymorphism would occur, or even if a polymorphism did occur, whether or not it would be associated with interstitial lung disease.

Quantity of Experimentation

In order to use the claimed polynucleotides and reagents, one would be required to undertake an extensive amount of experimentation to determine that a predictive association exists between any of the disclosed polymorphisms and any possible interstitial lung disease, or all interstitial lung diseases, as set forth in the claims. In view of the unpredictability of establishing a relationship between any single disease and a polymorphism, such study would require the screening of large numbers of patients. Furthermore, since the claims recite a generic association between polymorphisms in the human surfactant protein C gene and any interstitial lung disease, one would be required to screen for additional polymorphisms within the gene and establish a relationship between these polymorphisms as well as those disclosed herein and any of the various interstitial lung diseases. Such experimentation would be an enormous undertaking required prior to being able to use any reagents for detecting the thirty two polymorphisms disclosed herein for detecting polymorphisms "associated with interstitial lung disease (as recited in the claims)," or to make and use reagents for detecting polymorphisms yet undisclosed.

Conclusion

Thus, having considered carefully each of these factors, that is, the lack of a guidance or working examples in the specification demonstrating that any polymorphisms in human surfactant protein C genes are "associated with interstitial lung disease," particularly the elected SNP at position 243 of SEQ ID NO: 1, the high level of unpredictability in the related art, the high degree of experimentation necessary to establish a relationship between any of the disclosed SNPs and intersitital lung disease, and the breadth of the invention, it is concluded that undue experimentation would be required to use the claimed invention, and indeed to make the claimed invention insofar as it is unclear which of the SNPs disclosed herein and not yet disclosed are in fact "associated with interstitial lung disease."

13. Claims 9, 10, 14, 15, 16, 17, 19, and 20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

With regard to the physical structure of the products themselves, claim 9 encompasses a single-stranded polynucleotide comprising 12 contiguous nucleotides of a "mutant allele" of a human surfactant protein C gene, wherein the 12 contiguous nucleotides comprise a SNP associated with interstitial lung disease. While the claim recites that the 12 contiguous nucleotides must be from a "mutant allele" of a human surfactant protein C gene, the claim does not require that the 12 contiguous nucleotides overlap with the mutant SNP, only that the 12

contiguous nucleotide overlap with a SNP associated with interstitial lung disease. For example, a human surfactant protein C gene may be mutated at position 5, but the 12 contiguous nucleotides that are comprised within the claimed invention could be positions 15-26 which overlap with hypothetical polymorphic position 25, which, hypothetically is disclosed as being associated with interstitial lung disease, even if the particular human surfactant protein C gene is not mutated at position 25. The claim does not recite any polymorphisms in particular, and thus encompasses polynucleotides that overlap with any polymorphic position in the human surfactant C protein gene, provided the polymorphism is "associated with interstitial lung disease." In addition, the breadth of the claim encompasses SNPs within the human surfactant protein C gene that are associated with any "interstitial lung diseases" which include chronic pneumonitis of infancy, a variety of disorders associated with lung inflammation, pulmonary sarcoidosis, or lymphangitic carcinomatosis (infiltration and obstruction of pulmonary parenchymal lymphatic channels by tumor) (p. 6). These diseases all share in common that they are diseases of the lung interstita, but beyond that they represent a diverse group of diseases which have different causes and etiologies.

Claim 10, recites that the SNP is located at particular positions of SEQ ID NO: 1, with position 243 being elected for prosecution.

Claims 14-16 further define the claimed polynucleotide as comprising a label, having the SNP at the 3' or 5' end, and being on a solid support.

Claim 17 is drawn to a kit comprising a reagent for detecting a SNP in a mutant allele or a human surfactant protein C gene, wherein the SNP is associated with interstitial lung disease, and instruction for a method of detecting the SNP. The reagent of claim 17 encompasses a wide

variety of reagents, for example, polynucleotide probes that overlap with the SNP, restriction enzymes, sequencing reagents, labels, etc. The claim does not recite any polymorphisms in particular, and thus encompasses polynucleotides that overlap with any polymorphic position in the human surfactant C protein gene, provided the polymorphism is "associated with interstitial lung disease." In addition, the breadth of the claim encompasses SNPs within the human surfactant protein C gene that are associated with any "interstitial lung diseases" which include chronic pneumonitis of infancy, a variety of disorders associated with lung inflammation, pulmonary sarcoidosis, or lymphangitic carcinomatosis (infiltration and obstruction of pulmonary parenchymal lymphatic channels by tumor) (p. 6).

Claim 19 depends from claim 17 and recites that the reagent is a single-stranded polynucleotide comprising 12 contiguous nucleotides of a "mutant allele" of a human surfactant protein C gene, wherein the 12 contiguous nucleotides comprise the SNP or the complement of the SNP, and claim 20 recites that the SNP is located at particular positions of SEQ ID NO: 1, with position 243 being elected for prosecution.

The specification recites thirty two single nucleotide polymorphisms within the human surfactant protein C gene, but as discussed in the enablement rejection, the specification does not demonstrate which of these are "associated with interstitial lung disease," as required by the claims. Instant SEQ ID NO: 1 and nucleic acids consisting of fragments of SEQ ID NO: 1 that contain the polymorphic sites are described.

The claims, being drawn using "comprising" language encompass polynucleotides that have as few as 12 nucleotides in common with the human surfactant C protein, but are contained within any context, as exemplified by the prior art applied under 102 which is a sequence that is

from a dog. The structural language in the claims encompasses a vast array of possible polynucleotides that are not described in the specification. Applicant has not demonstrated possession of any possible polynucleotide that **comprises** 12 contiguous nucleotides of any version of a human surfactant protein C gene that contains a SNP associated with intersititial lung disease, since there are hundreds of thousands of possible nucleic acids that comprise such nucleic acids. This rejection applies to claims 10 and 20 insofar as they are also drawn using "comprising" language. Amendment of these claims to clarify that the claimed polynucleotide "consists of" a fragment of instant SEQ ID NO: 1 that includes position 243 (elected SNP) of instant SEQ ID NO: 1 would overcome this rejection with regard to claims 10 and 20.

In addition, the generic claims include polynucleotides that comprise or reagents that detect any polymorphism within the human surfactant C gene that is associated with interstitial lung disease. The specification has described thirty two possible polymorphisms, but these are not joined by any structural characteristic such that one could readily predict other possible polymorphisms within this gene, either in the coding region as given in SEQ ID NO: 1, or in the genomic sequence which is not recited in the specification. The "functional language" that defines these SNPs as being associated with interstitial lung disease does not lead one to a predictable structure that would allow one to determine even which of the 32 polymorphisms disclosed in the specification meet the requirement of being "associated with interstitial lung disease," let alone any SNP that has not been described explicitly in the specification.

Because of these deficiencies, the claims are rejected as lacking adequate written description.

Conclusion

14. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (703) 306-5824. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Juliet C Switzer
Examiner
Art Unit 1634

September 25, 2003